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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,686	03/09/2001	Gary Van Nest	377882000900	9981

25226 7590 09/24/2002

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/802,686	Applicant(s) VAN NEST, GARY	
	Examiner Richard Schnizer	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for reconsideration was received and entered as Paper No. 12 on 6/24/02.

Claims 1-15 are pending and under consideration in this Office Action.

The art unit and Examiner in charge of this Application have changed. Please address further correspondence to Richard Schnizer, AU 1635, whose full contact information is given at the conclusion of this Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record in Paper No. 8.

The instant claims are drawn to a method of suppressing a respiratory syncytial virus (RSV) infection in an individual by administering a composition containing a poly-nucleotide comprising an immunostimulatory sequence (ISS) wherein composition does not contain RSV antigen. Claims are further directed to a kit containing polynucleotide comprising ISS.

The instant invention is to an effective treatment for respiratory syncytial virus (RSV) infection where virus replication virus is inhibited by administration of ISS sequences without administration of any antigen. It is noted that the working example 2 & 3 teach local and non-local administration of ISS sequences in rats. For local administration, rats were administered with 150 microgram of oligonucleotide comprising ISS sequence (SEQ.ID NO.1) intra-nasally. Thirty minutes later, animals were inoculated with infectious dose of RSV ($TCID_{50}$). Control group had same amount of control nucleotide sequence (SEQ. ID. NO.9 & 10) and were also inoculated similarly. For non-local administration, rats were administered with the same amount of ISS and control sequences intraperitoneally (IP) or sub-cutaneously (SC). Reduction in virus titer was shown in the lung samples of experimental rats in case of local administration (Fig. 1 and table 2), as compared to non-local administration (table 4 & 5). The specification also teaches similar working examples for influenza virus using ISS SEQ. ID. NO.1 and control oligonucleotide SEQ. ID. NO. 9 & 10 and shows reduced titer of virus in the lung samples (Table 7 & 9). However, claims are not enabled for a method that suppresses the infection in all mammals using ISS sequences. The specification also fails to provide the guidance to use the claimed polynucleotide ISS comprising the sequence (5'-T C G -3'), (5'- AACGTTCC-3'), (5'-AACGTTCG-3'), (5' GACGTTCC-3') and (5'-GACGTTCG-3') in the working examples.

The state of the art at the time of filing is well known for ISS sequences. However the prior art teaches only an adjuvant role of ISS sequences and is shown to stimulate immune response to co-administered antigens in case of several different pathogens.

Thus it is not predictable that one of skill in the art could achieve efficient antiviral effect of ISS polynucleotide in case of said viral infection. At the time of filing, the relevant art considered antiviral chemotherapy and chemoprophylaxis to be unpredictable because sufficient antiviral effect to provide an alleviation of symptoms related to said virus had not been developed. Two references are cited herein to illustrate the state of art of antiviral effect of two compounds: *Amantadine* and *Rimantadine* for respiratory and influenza viral infections. Dolins (1985) recites: "although *amantadine* has been generally well tolerated by the populations in which it has been studied, variable rates of side effects have been reported (See column 4, pg. 1297)." He further recites: "although *Rimantadine* appears to be nontoxic and effective in uncomplicated cases, its efficacy in the treatment of more serious disease has yet to be proved (See Column 7, pg. 1298)." Shigeta (1998) recites: Although the prophylactic use of *Amantadine* and *Rimantadine* for influenza A virus has been recommended. However, there is a continuing need for more effective antiviral agents to manage viral acute respiratory infections (See Conclusion, pg.104). Thus to overcome these teachings in the art, the specification would need to show an effective treatment in alleviating a symptom of said virus by the claimed ISS sequences.

In the instant case, applicant claims a method of suppressing a respiratory syncytial virus (RSV) in an individual by administering a polynucleotide containing ISS sequences. The working example set forth discloses inhibition in replication of the virus in lung samples of experimental animals. However, the results do not indicate that any of the symptoms of respiratory infection is ameliorated. The relatively simple structure of

viruses does not mean that they are easy targets for chemotherapy. In addition, the replication cycle of a virus is associated with the host cell's biochemical pathways, good selectivity is difficult to achieve. Replication cycle of said viruses will vary from one host to another. Also the attack rate for said virus will vary from outbreak to outbreak. Therefore, amount of each polynucleotide needed to suppress the infection will vary in each case tremendously. While animal models are valuable tools for the design of experiments, these models, such as mouse or rat models do not mimic relevant human conditions. One cannot predict similar results in case of other hosts. Applicant recites different ISS polynucleotides of different length. There are no working examples showing the administration of other ISS polynucleotide in the animals. Because of the difference in length, a dosage amount of ISS polynucleotide will also vary among different species of mammals.

Thus, considering the lack of prior state of the art and without guidance not provided in the specification, the skilled artisan at the time of filing would be lacking a reasonable expectation of success for a method of suppressing a respiratory syncytial virus infection in an individual by administering a composition of polynucleotide comprising an immunostimulatory sequence, without an undue amount of experimentation.

Response to Arguments

Applicant's arguments filed 6/24/02 have been fully considered but they are not persuasive.

In the paragraph bridging pages 2 and 3 of the response, Applicant addresses the Examiner's position that the results do not indicate amelioration of any symptoms. Applicant asserts that the claims require only suppression of syncitial virus infection, and that the specification teaches that suppressing viral infection "indicates any aspect of viral infection such as viral replication, time course of infection, amount (titer) of virus, lesions, and/or one or more symptoms is curtailed inhibited, reduced (in terms of severity and/or duration)...." Applicant concludes that the claims are not limited to any single aspect listed above and Applicant is not required to show every aspect listed above. The Examiner agrees, however it is noted that for the full scope of the claims to be enabled, the invention must function to suppress each of these aspects in some embodiment. Although the Examiner presented evidence of the unpredictability of treating viral infections, Applicant has presented no evidence or argument that each of the aspects listed above is enabled, thus at best only the aspect of reducing viral titer is enabled. However, further analysis of the data concerning reduction of viral titer indicates that this aspect of the invention also lacks enablement. As noted in the rejection, the specification contains several working examples with results set forth in Fig. 1 and Tables 2, 4, 5, 7, and 9. The specification teaches that administration of ISS oligonucleotides as shown in Tables 4, 5, 7, and 9 fail to cause any significant reduction in viral titers compared to PBS control. See page 42, lines 3-5, page 43, lines 1-3, and page 44, lines 6-9. Fig. 1 shows a viral titer of 12,000 per gram of lung for a PBS control, compared to a titer of less than 1000 for administration of ISS. However, Fig. 1 shows no statistical analysis. On the other hand Table 2 reports the same data but

indicates that the results are "not quite statistically significant". Thus all of the available evidence of record indicates that the claimed invention does not function to produce a statistically significant effect on viral titer.

In the paragraph bridging pages 3 and 4 of the response, Applicant addresses the Examiner's concerns regarding the scope of polynucleotides embraced by the invention. Applicant notes that SEQ ID NO:1 used in the examples is representative of the claimed genus. This argument is unpersuasive because, the working examples failed to show any significant effect on viral infection

At page 4 of the response Applicant notes that the burden is on the Office to establish a prima facie case of non-enablement, and that the specification must be considered to be enabling in the absence of a reasons to doubt the objective truth of the disclosure. In this case, all of the available evidence, (the working examples) demonstrate that the invention does not function as intended. This provides ample reason to doubt the enablement the objective truth of the disclosure, and provides proof that that the specification is not enabling for the entire scope of the invention as claimed.

At pages 5 and 6 of the response, Applicant addresses the significance Dolins and Shigeta references relied upon by the Examiner, and concludes that no evidence has been produced to establish that the teachings of the specification would not enable one of skill in the art to practice the invention without undue experimentation. However, as noted above, the available evidence of record supports the unpredictability of the art by showing that the claimed invention does not function as intended. Applicant notes

that the specification at page 40,lines 6-10 indicates that the treatment caused a reduction in viral titer, but as noted above, Table 2 indicates that any reduction was not statistically significant.

For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

~~PRIMARY EXAMINER~~

JAMES KETTER
PRIMARY EXAMINER